

Clinical Investigations

Continuous Versus Intermittent Infusion of Furosemide in Acute Decompensated Heart Failure

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ABSTRACT

Background: Despite advances in the treatment of chronic ambulatory heart failure, hospitalization rates for acute decompensated heart failure (ADHF) remain high. Although loop diuretics are used in nearly all patients with ADHF to relieve congestive symptoms, optimal dosing strategies remain poorly defined.

Methods and Results: This was a prospective, randomized, parallel-group study comparing the effectiveness of continuous intravenous (cIV) with intermittent intravenous (iIV) infusion of furosemide in 56 patients with ADHF. The dose and duration of furosemide as well as concomitant medications to treat ADHF were determined by physician preference. The primary end point of the study was net urine output (nUOP)/24 hours. Safety measures including electrolyte loss and hemodynamic instability were also assessed.

Twenty-six patients received cIV and 30 patients received iIV dosing. The mean nUOP/24 hours was 2098 ± 1132 mL in patients receiving cIV versus 1575 ± 1100 mL in the iIV group ($P = .086$). The cIV group had significantly greater total urine output (tUOP) with 3726 ± 1121 mL/24 hours versus 2955 ± 1267 mL/24 hours in the iIV group ($P = .019$) and tUOP/mg furosemide with 38.0 ± 31.0 mL/mg versus 22.2 ± 12.5 mL/mg ($P = .021$). Mean weight loss was not significantly different between the groups. The cIV group experienced a shorter length of hospital stay (6.9 ± 3.7 versus 10.9 ± 8.3 days, $P = .006$). There were no differences in safety measures between the groups.

Conclusions: The cIV of furosemide was well tolerated and significantly more effective than iIV for tUOP. In addition, continuous infusion appears to provide more efficient diuresis. (*J Cardiac Fail* 2010;16:188–193)

Key Words: Diuretics, furosemide, heart failure.

Chronic heart failure (HF) is the leading cause of hospitalization in patients older than age 65 in the United States with more than 1 million admissions annually.¹ Most patients admitted with acute decompensated heart failure (ADHF) present with dyspnea and edema from volume

retention. Although there have been several advances in the treatment of ADHF, intravenous (IV) loop diuretics are the most common therapy used to treat excessive volume overload.² Though efficacious, loop diuretics have been associated with detrimental effects in the HF population. A retrospective review of the Studies of Left Ventricular Dysfunction dataset noted an increased risk of hospitalization, all-cause mortality, and cardiovascular death associated with the use of non-potassium-sparing diuretics.³ The Heart Failure Society of America's guidelines for management of ADHF also note the adverse outcomes associated with the use of diuretic therapy and recommend the lowest doses necessary to provide adequate symptom relief.⁴

Despite near universal use in this setting, the ideal strategy for initial diuresis remains unclear. Theoretically, continuous infusion of a loop diuretic would avoid the increased sodium reabsorption in the distal tubule seen commonly after bolus dosing as the concentration drops below the threshold for

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Manuscript received March 19, 2009; revised manuscript received November 11, 2009; revised manuscript accepted November 24, 2009.

The authors have no conflicts of interest.

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1071-9164/\$ - see front matter

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doi:10.1016/j.cardfail.2009.11.005

natriuresis. In addition, continuous infusion should allow for more consistent diuresis, avoiding wide swings in intravascular volume and their possible attendant neurohormonal activation. Lower peak serum concentrations afforded by continuous dosing could potentially mitigate some of their adverse effects, especially at higher doses.

Continuous infusion of furosemide has shown less variability in hourly diuresis but with no significant difference in overall efficacy compared with intermittent dosing in cardiac surgery patients.⁵ However, studies examining the effects of furosemide on neurohormonal response in patients with HF have found no difference between continuous infusion and intermittent dosing.^{6,7}

Studies comparing the efficacy and safety of continuous with intermittent IV infusion of loop diuretics in ADHF have yielded conflicting results and lack clinically relevant outcomes information to allow specific recommendations to be made.⁸ Previous studies have also used inconsistent or overly regimented dosing strategies not well translated to everyday clinical practice.

Published data demonstrate continued need to explore dosing regimens that will optimize patient outcomes. The study design for the large, ongoing Diuretic Optimization Strategies Evaluation (DOSE) trial being conducted by the National Institutes of Health Heart Failure Clinical Research Network has recently been published.⁹ This study uses a 2 × 2 factorial design to evaluate continuous versus intermittent dosing of furosemide at low versus high intensification of dosing. In the present study, we sought to examine the clinical efficacy and safety of continuous versus intermittent administration of IV furosemide in a less regimented, real-world clinical setting.

Methods

Study Design

This was a prospective, randomized, parallel-group pilot study comparing continuous with intermittent infusion of furosemide in patients admitted to 2 tertiary-care medical centers with a diagnosis of ADHF. Patients were excluded from the study if they had received more than 2 doses of intravenous furosemide before randomization. This trial was approved by each institution's investigational review board.

After screening for eligibility and written informed consent, patients were stratified based on serum creatinine at the time of admission (≤ 2.5 versus > 2.5 mg/dL). Randomization occurred separately at each institution and in each stratum in blocks of 10. Group assignments were contained in individual sealed envelopes located at each institution.

The specific doses of furosemide and the use of additional agents to manage ADHF (thiazide diuretics, inotropes, IV vasodilators, nesiritide) were allowed as deemed medically necessary by the treating physician. The frequency of laboratory determinations of electrolytes and renal function as well as electrolyte supplementation was left to the discretion of the treating physician.

Patient Population

Patients older than age 18 years with ADHF requiring an anticipated 36-hour minimum duration of IV diuretic therapy were

eligible for inclusion. Patients were excluded if they had received greater than 2 IV doses of furosemide or any continuous infusion of furosemide before randomization. Cumulative intake (oral and IV) and urine output were determined by daily review of nursing intake and output flowsheets for each subject while on study medication, extending to the end of the shift during which study medication was terminated.

Outcomes Measures

The primary efficacy end point was net daily urine output (nUOP), defined as urine output minus oral plus IV intake normalized per 24 hours. Secondary end points included the following: net daily UOP normalized for amount of furosemide received (nUOP/mg furosemide), total daily urine output (tUOP), total daily urine output normalized for amount of furosemide received (tUOP/mg furosemide), weight loss during the study, need for additional ADHF therapy (eg, thiazide diuretic, nesiritide, inotropes), duration of study drug administration, and length of hospitalization.

The primary safety measures were the daily amount of potassium and magnesium supplementation required during IV furosemide administration and increases in serum creatinine of 0.5 mg/dL or greater. We also documented significant hypotension (systolic blood pressure < 85 mm Hg), and the number of held doses of antihypertensive medications as another indicator of hypotension.

Data Analysis

All data were analyzed by intention-to-treat. Continuous variables are presented as mean \pm standard deviation unless otherwise mentioned and are compared using the Students *t*-test (2-tailed), unpaired. Differences between treatment groups for the categorical variables were analyzed using the chi-square test. For the purposes of this study, *P* values $\leq .05$ were considered significant. Only 4 patients had a serum creatinine > 2.5 mg/dL; consequently, these patients were not analyzed separately, but were added to the corresponding group of patients with SCr ≤ 2.5 mg/dL to which they were randomized.

Results

A total of 57 patients were randomized. One patient was excluded from final data analysis because of an incomplete consent form. There were 26 patients randomized to receive continuous intravenous (cIV) and 30 patients randomized to receive intermittent intravenous (iIV) administration of furosemide.

Baseline Characteristics

Table 1 provides patient characteristics at the time of enrollment. More patients randomized to receive iIV therapy required inotrope support before enrollment; however, this did not reach statistical significance. Patients randomized to the cIV group received more IV furosemide before enrollment (94 versus 58 mg).

Efficacy Analysis

The mean daily dose of furosemide was 197 ± 148 mg and 172 ± 97 mg in the cIV and iIV groups, respectively

Table 1. Baseline Characteristics

	cIV Group (n = 26)	iIV Group (n = 30)	P Value
Age, mean (range), y	56.4 (23-79)	54.6 (18-88)	.85
Race, n (%)			
Caucasian	13 (50)	16 (53)	.7
African American	13 (50)	14 (47)	
Sex, n (%)			
Male	15 (62)	17 (81)	.85
Female	10 (38)	4 (19)	
Baseline SCr, mean (SD), mg/dL	1.73 (0.85)	1.54 (0.51)	.37
SCr > 2.5 mg/dL, n (%)	3 (11.5)	1 (3.3)	.23
NYHA classification, n (%)			
III	10 (38)	11 (37)	.59
IV	9 (35)	11 (37)	
Not reported	7 (27)	7 (23)	
Ejection fraction, mean (SD), %	29 (13.7)	24 (13.4)	.18
Chronic oral furosemide dose, mean (SD), mg/day	114.2 (72.6)	105.9 (60.2)	.9
Other medications at randomization, n (%)			
ACE inhibitors	19 (73)	20 (67)	.6
ARBs	8 (31)	4 (13)	.11
ACEI + ARB	1 (4)	0 (0)	.28
β -blockers	18 (69)	25 (83)	.21
Hydralazine	6 (23)	6 (20)	.78
Nitrates	9 (35)	6 (20)	.22
Inotropes	1 (4)	6 (20)	.068
Number of doses of furosemide received before study, (n) mean (SD)	1.3 (0.84)	0.83 (0.83)	.017
Furosemide dose received before study, (mg) mean (SD)	94 (70.7)	58 (62.6)	.03

cIV, continuous infusion furosemide; iIV, intermittent infusion furosemide; SCr, serum creatinine; NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

($P = .46$). The mean duration of study drug administration tended to be shorter by approximately one day in the cIV group; however, this was not statistically significant (86.4 ± 50.5 hours versus 112.5 ± 73 hours, $P = .12$). Two patients in the iIV group were crossed over into the continuous infusion group and 1 patient in the cIV group received intermittent dosing. Removal of these patients in an as-treated analysis did not affect the overall results.

The mean nUOP/24 hours was 2098 ± 1132 mL in patients receiving cIV versus 1575 ± 1100 mL in the iIV group ($P = .086$). The cIV of furosemide was associated with a greater diuresis with tUOP of 3726 ± 1121 mL/24 hours compared with 2955 ± 1267 mL/24 hours in the iIV group ($P = .019$). The tUOP/24 hours and nUOP/24 hours between the 2 groups are shown in Fig. 1. When normalized for the amount of furosemide received, the cIV group had a mean daily tUOP of 38 ± 31 mL/mg of furosemide versus 22 ± 13 mL/mg in the iIV group ($P = .021$). The difference in the nUOP/mg furosemide received favored continuous infusion, but did not reach significance (cIV group, 17.4 ± 18.5 mL/mg versus iIV group, 11.6 ± 10.5 mL/mg, $P = .178$).

A similar number of patients in both groups were treated with additional agents for ADHF, including thiazide diuretics (chlorothiazide and metolazone), inotropes (milrinone and dobutamine), and vasodilators (nesiritide). Both groups experienced a significant degree of weight loss during the study. The cIV group lost an average of 6.8 ± 6.1 kg and the iIV group lost an average of 5.1 ± 4.6 kg ($P = .24$). The use of a continuous infusion of furosemide was associated with a shorter length of hospital stay, 6.9 ± 3.7 days,

compared with 10.9 ± 8.3 days in the iIV group ($P = .006$). Secondary outcomes are presented in Table 2.

Safety Analysis

Though not mandated by the study protocol, both groups had similar frequency of laboratory determination of electrolytes and renal function (98% of patient days in the cIV versus 97% of patient days in the iIV group). Both cIV and iIV groups required similar amounts of potassium replacement. There was a nonsignificant trend toward higher magnesium replacement in the cIV group. There were 5 patients in each treatment group who experienced an increase in serum creatinine by 0.5 mg/dL or greater. Though not prespecified secondary end points, there was

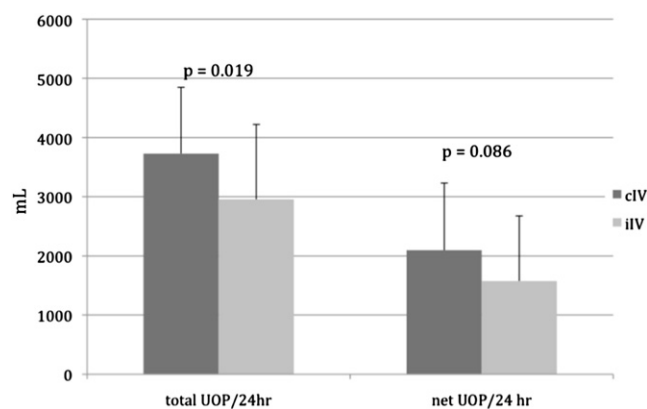


Fig. 1. Efficacy outcomes: mean total daily urine output and mean net daily urine output with continuous (cIV) versus intermittent (iIV) intravenous administration of furosemide.

Table 2. Secondary Efficacy End Points

	cIV Group (n = 26)	iIV Group (n = 30)	P Value
Net UOP/mg furosemide, mean (SD), mL/mg	13.74 (13.26)	10.37 (9.62)	.18
Total daily UOP/mg furosemide, mean (SD), mL/mg	38.0 (31.1)	22.2 (12.7)	.021
Additional ADHF therapy, n (%)			
Thiazide diuretic	9 (35)	10 (33)	.91
Inotrope	5 (19)	10 (33)	.23
Nesiritide	2 (8)	2 (7)	.88
Weight loss during study, mean (SD), kg	6.8 (6.1)	5.1 (4.6)	.24
Duration of IV furosemide, mean (SD), h	86.4 (50.5)	112 (73)	.12
Length of hospitalization, mean (SD), days	6.9 (3.7)	10.9 (8.3)	.006
SCR >0.5 mg/dL increase during study, n (%)	5 (19)	5 (17)	.19

cIV, continuous infusion furosemide; iIV, intermittent furosemide dosing; UOP, urine output; SCR, serum creatinine.

a statistically significant difference favoring the cIV group in the maximum increase from baseline of serum creatinine but not blood urea nitrogen (Fig. 2). No patients in either group required hemodialysis or ultrafiltration. There was also no difference in the incidence of hypotension or degree of decrease in systolic blood pressure between the groups. Safety results are summarized in Table 3. There was 1 death during the study. It was unrelated to ADHF treatment and occurred as a complication of heart transplantation.

Discussion

In this prospective, randomized trial, there was no significant difference in the primary outcome measure, defined as net daily UOP. However, there were significant differences favoring the cIV group with regard to total daily UOP, total daily UOP/mg furosemide, maximum increase in serum creatinine, and length of hospitalization. The other secondary end points favored the cIV group, but did not reach statistical significance.

The current study is unique in several ways. Compared with published trials, it was larger and had a longer duration of treatment (mean, 4.18 days). The design allowed many additional treatments affecting urine output. These additional treatments were purposefully not controlled, thus mimicking “real-world” clinical practice. Though this could be seen as a design limitation, the randomization process maintained relative homogeneity between groups.

To affect natriuresis and diuresis, all loop diuretics must be filtered and secreted to their site of action on the luminal side of the loop of Henle. In patients with HF, the dose-response curve is shifted to the right, often with a blunted maximal response.¹⁰ This necessitates higher dosing for efficacy. Despite escalating doses, diuretic resistance remains a common problem in treating patients with ADHF. The mechanisms by which diuretic resistance occurs involve specific drug pharmacokinetics and physiologic adaptations within the nephron. These include postdiuretic sodium rebound, resulting in increased sodium reabsorption after diuretic levels fall below the threshold to maintain natriuresis¹⁰ and the “braking phenomenon”^{10,11} in which the response to subsequent doses of a loop diuretic are diminished. This may be a result of renin secretion from the macula densa as well as sympathetic nerve stimulation resulting from diuretic-induced intravascular volume loss. Last, hyperplasia and hypertrophy of the thiazide sensitive cells in the distal convoluted tubule occurs with long-term diuretic use.¹² This results in increased distal sodium resorption limiting the effect of loop diuretics.

In theory, continuous infusion of a loop diuretic could maintain levels above the natriuretic threshold and provide more constant diuresis without wide swings in intravascular volume. These are characteristics that could potentially obviate two of the known mechanisms of diuretic resistance. In the current study, despite more total diuresis in the cIV group, the maximum increase in serum creatinine was significantly greater in the iIV group.

Despite the theoretical advantages noted previously, the literature comprising randomized clinical trials comparing continuous versus intermittent bolus administration of loop diuretics are limited in number, size, and length of therapy. A meta-analysis of 7 randomized controlled trials comparing efficacy of continuous versus bolus intravenous

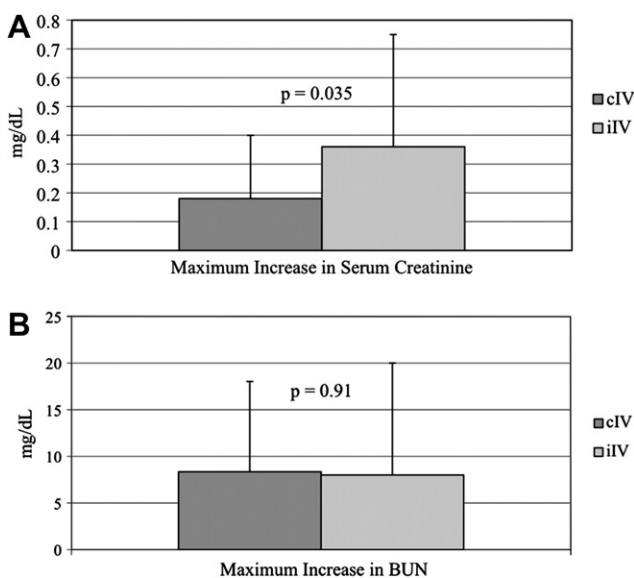


Fig. 2. Maximum increase from baseline in serum creatinine (SCr) mean ± SD, (A) and maximum increase from baseline in blood urea nitrogen (BUN) mean ± SD (B).

Table 3. Safety Evaluation

	cIV Group (n = 26)	iIV Group (n = 30)	P Value
Potassium replacement, mean (SD), mEq/day	34 (30)	2 (32)	.86
Magnesium replacement, mean (SD), mg/day	425 (783)	177 (354)	.078
Patients requiring antihypertensive doses held, n (%)	7 (26)	8 (27)	.98
Patients with significant hypotension, n (%)	9 (35)	11 (37)	.87
Lowest SBP, mean (SD), mm Hg	98.9 (18.5)	93.8 (19.9)	.14
Patients with increase in serum creatinine, n (%)	5 (19)	5 (17)	.53

cIV, continuous infusion furosemide; iIV, intermittent infusion furosemide; SBP, systolic blood pressure.

infusion of loop diuretics in heart failure noted greater urine output (measured as mL/24 hours) in patients given furosemide by continuous infusion.⁸ There were no significant differences in electrolyte abnormalities and adverse effects were fewer in the continuous infusion group. Many of the reviewed trials were of crossover design without adequate reequilibration between treatment arms. The authors circumvented this limitation by including only data derived from the initial treatment allocation. The authors concluded “The poor quality of currently available data cannot be over emphasized. Thus robust recommendations for clinical practice still cannot be made at this time.”⁸

Results from the current study are in agreement with results from four smaller studies conducted in patients with HF, all of which employed randomized crossover design. Dormans et al⁷ used high doses of furosemide given as a single bolus or as a 20% bolus followed by continuous infusion over 8 hours in 20 patients. There was a significant increase in daily urine volume with continuous infusion (2860 ± 240 mL versus 2260 ± 150 mL, $P = .0005$). In a study by Lahav et al (n = 8),¹³ bolus dosing was administered 3 times daily. Infusion dosing was begun with a bolus injection followed by continuous infusion. Crossover was immediate without a washout. Total urine output over 48 hours was significantly higher in the infusion group (mean 4490 mL versus 3790 mL, $P < .01$). Though the study duration was longer, similar to the current study, the lack of an adequate washout period hampers interpretation of these data.

Two additional studies have shown marginally greater diuresis with continuous versus bolus administration of furosemide (n = 20)¹⁴ and torsemide (n = 8)¹⁵ in HF patients. As with Lahav et al, interpretation of these studies is limited by their crossover design without an appropriate washout and short duration of administration and urine collection.

In another crossover study, Aaser et al¹⁶ found no significant difference in urine output in 8 patients randomly assigned to continuous versus bolus IV administration of furosemide. Treatment and urine collection was limited to 24 hours. Unlike the studies by Dormans and Lahav, a bolus dose was not administered before initiation of the continuous infusion. This, the small sample size reported, and the relatively short duration of treatment may explain their differing results. Although a bolus immediately before continuous infusion was not mandated in our study, the duration

of treatment should have mitigated this potential confounder.

Although there were no significant differences in safety measures in our study, magnesium replacement was three fold higher in the cIV compared with the iIV group and warrants mention. The lack of statistical significance is likely attributable to the small sample size and large standard deviation noted. Nevertheless, this finding is clinically significant and in agreement with Pivac et al,¹¹ who noted increased magnesium excretion with continuous versus bolus administration of furosemide.

The finding of a significantly shorter length of hospital stay in the continuous infusion group is interesting, especially with no significant differences noted in duration of study drug administration and weight loss between the 2 groups. Sample size may have contributed to this finding. However, with the average duration of study drug administration only half the average length of stay, perhaps some initial gains were compromised during the transition to oral diuretic therapy before discharge. There were also factors unrelated to diuresis, such as prolonged hospitalization for implantable cardioverter defibrillator placement or transplant evaluation that were not systematically collected but were noted to occur.

Limitations

Although patients were randomly assigned to treatment groups, the study was not blinded and though the groups were similar in many respects, there were also some significant baseline differences that were likely the result of the relatively small sample size. Patients in the cIV group had received more furosemide and had a higher mean serum creatinine at the time of randomization, perhaps indicative of a population more prone to diuretic resistance and cardiorenal syndrome. This may have biased the results in favor of the cIV group. However, despite more total diuresis, the cIV group experienced a smaller increase in creatinine during the study making this an unlikely confounder. Receiving more furosemide before randomization could have influenced the differences noted in study duration and length of stay.

More patients receiving intermittent dosing were receiving inotropes at the time of randomization, possibly marking a sicker population. Because the initiation and discontinuation of inotropes and IV vasodilator treatment

was not controlled, it is difficult to speculate on any bias that may have resulted.

Although it is one of the larger trials of its kind to date, the current trial was underpowered to detect a difference in the primary end point, net urine output/24 hours. This end point was selected because of its clinical relevance in treating patients with ADHF. By design, many factors that may have contributed to nUOP, particularly IV intake, were not controlled, perhaps biasing our findings. Although not statistically significant, this and other secondary end points dependent on net fluid balance (weight loss, duration of treatment) trended in favor of continuous infusion. In general, the renal function of patients was fairly well preserved, so the application of these data may not be appropriate for patients with moderate to severe renal insufficiency.

Conclusion

The continuous administration of furosemide was well tolerated and more effective than intermittent dosing for total daily urine output. In addition, the efficiency of diuresis as measured by urine output/mg furosemide appears to be greater with continuous dosing with less worsening of serum creatinine during therapy. Although there were no significant differences in safety measures, continuous infusion of furosemide was associated with more magnesium replacement.

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